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ON THE MODE OF ACTION OF LYMPHAGOGUES.

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(Plate I., and 1 Figure in Text.)

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In a paper published last year under a similar title[1] I recorded the results of experiments made in Heidenhain's laboratory in 1892, dealing with the action of 'peptone' on lymph-formation. From the fact that, after the injection of peptone into the circulation, the percentage amount of peptone in the lymph might rise above that in the blood, I concluded that peptone acted as a specific stimulus to the endothelial cells of the blood vessels, and that, as Heidenhain had concluded from a long series of experiments, the lymph was to be looked upon as a secretion rather than as a transudation.

Since the publication of the above, a renewed examination[2] of Heidenhain's experiments involving mechanical interference with the circulation has shown that these experiments do not justify his conclusions, and that in fact their results may be explained if we look upon lymph-production as dependent on two factors—viz., intracapillary pressure and permeability of the vessel wall. It became imperative then to submit the action of lymphagogues to a fresh investigation in order to see how far the conclusions arrived at in my paper "On the Influence of mechanical Factors on Lymph-formation" hold good when applied to the explanation of the action of these bodies.

The lymphagogues described by Heidenhain[3] are substances which, injected into the blood-stream, cause an increased flow of lymph from the thoracic duct. He divides them into two classes.

The first class includes substances such as peptone, leech extract, cray-fish extract, etc. These bodies cause an increased flow of more concentrated lymph. The plasma of the blood is diminished in quantity.

[1] This *Journal*, xiv. 131, 1893. [2] This *Journal*, xvi. 224, 1894.

[3] "Versuche und Fragen zur Lehre von der Lymphbildung." *Pflüger's Archiv*, xlix. p. 209.

and the amount of solids it contains is also diminished. Long continued obstruction of the thoracic aorta annuls their action (from injury to the secretory endothelium of the abdominal vessels). The increased lymph-flow is derived from the blood.

The second class includes crystalloids such as sugar, salt, etc. These increase the lymph-flow, the lymph becoming more watery than before. The blood at the same time becomes also more watery, so that the excess of lymph cannot be derived from the blood but must come from the tissues. Some time after the injection of sugar, the percentage amount of this substance in the lymph rises higher than that in the blood plasma. Long continued obstruction of the aorta does not annul the action of these bodies. I will commence with a discussion as to the mode of action of substances belonging to this class, since they are simpler both in their constitution and their effects than the members of the first class of lymphagogues.

The Second Class of Lymphagogues.

Heidenhain would explain the action of these substances in the following way. When the blood containing a large excess of, say, sugar arrives at the capillaries, the cells forming the walls of these tubes seize on the sugar and excrete it on the other side into the lymph-spaces. Arrived here in a concentrated solution it robs the tissues of water, so that the volume of the interstitial fluid is largely increased, and the excess flows away and gives rise to the largely increased lymph-flow. At the same time water passes from lymph to blood by a process of diffusion (?) and the blood also becomes largely diluted. According to Heidenhain, the increased lymph-flow cannot be brought about by a process of filtration, since the arterial pressure is practically unaltered by the injection of sugar.

In previous papers however I have insisted on the absolute inadequacy of a simple determination of the arterial pressure to decide the question whether the lymph-flow is or is not determined by intracapillary pressure. Thus, for example, in hydræmic plethora, the arterial blood-pressure is almost unchanged. Under these circumstances however, as Bayliss and I have shown[1], there is a large rise of pressure in the portal vein and vena cava, and a corresponding rise of pressure in the capillaries of the abdominal organs, and I have shown that the increased lymph-flow is determined almost entirely by the rise of

[1] This *Journal*, XVI. 181, 1894.

capillary pressure and hardly at all by the altered constitution of the blood.

Now we know already that the injection of large amounts of sugar into the circulation gives rise to a condition of hydræmic plethora. In von Brasol's experiments[1], the dilution of the blood caused by the injection of sugar was determined from estimations of the hæmoglobin in the blood before and after the injection. In one experiment, the hæmoglobin sank to 31 %, and in many cases, to 50—57 % of its original height, so that the volume of the circulating blood must have been doubled or trebled. In a dog weighing 7 kilos. a doubling of the volume of the blood would be equivalent to the injection of 500 c.c. normal saline. We might therefore predict that the injection of sugar would cause a rise of pressure in portal vein and vena cava similar to that produced by the injection of large quantities of normal saline. Such indeed is the case. I give here a shortened protocol of one experiment.

Bitch, 8 kilos.

Time	Fem. art.	Portal vein	Inf. cava
11.15	100 mm. Hg.	80 mm. $MgSO_4$	12 mm. $MgSO_4$
11.16—11.20	40 grams dextrose in water (50 c.c. fluid) injected.		
11.20	65	210	180
11.30	105	147	50
11.40	120	120	25
11.50	118	120	17
12.0	114	124	18
12.15	107	126	18

To compare with this I give an experiment in which the lymph-flow was measured. (Cp. Pl. I., fig. 1.)

Dog, 12 kilos. Kidney vessels ligatured.
Lymph in 10 minutes.

3—3·6* || 33—31—20—12—9—8·4—6·4

* 30 grams dextrose in 30 c.c. water injected into jugular vein.

We see then that injection of sugar causes a great rise of pressure in the capillaries of the abdominal organs, and coincidently with this rise of capillary pressure there is a great increase in the lymph-flow from the thoracic duct.

There are two factors here which might cause the increased flow of lymph, viz. (1) the presence of a concentrated solution of sugar in the

[1] *Du Bois' Archiv*, 211, 1881.

blood (the effective factor according to Heidenhain), and (2) the rise of capillary pressure. Which of these is responsible for the increased lymph-flow?

We can decide this question in the same way as we settled the analogous one in treating of hydræmic plethora[1]. The dilution of the blood which follows the injection of sugar is due to an attraction of water from the tissues. The blood-plasma has an osmotic pressure = ·92 % NaCl solution. When we increase its osmotic pressure by the injection of concentrated solutions of sugar, there will be an attraction of water from the tissues into the blood until the osmotic pressures are once more equalised on the two sides of the vessel-wall. If, for instance, we inject 10 c.c. of a 10 % solution of salt, it will attract water from the tissues until it is diluted to ·92 %, so that, roughly speaking, injection of 10 c.c. of a 10 % solution will increase the volume of the circulating blood by 100 c.c. The molecular weight of dextrose is about three times that of sodium chloride. The osmotic coefficient of sodium chloride is nearly double that of dextrose, so that a 6 % solution of dextrose will be approximately isotonic with a 1 % solution of sodium chloride. On injection of a strong solution of dextrose into the circulation, water will pass from tissues into the blood, until the original solution injected has been diluted to 6 %. Injection of 6 grms. dextrose is therefore equivalent to the injection of 100 c.c. normal salt solution. These considerations will render the two following experiments intelligible.

In the first experiment, a dog weighing 7 kilos. was bled to 240 c.c. 18 grms. dextrose dissolved in water, making 20 c.c. fluid altogether, were then injected. The effect of this was the same as if 300 c.c. normal saline had been injected[2]. All the pressures, arterial and venous, returned to their previous height, showing that the volume of circulating fluid was approximately the same as before. I give here a shortened protocol of this experiment.

Time	Fem. art.	Portal vein	Inf. cava
11.45	101 mm. Hg.	78 mm. $MgSO_4$	30 mm. $MgSO_4$
Dog bled to 240 c.c.			
11.50	61	45	8
11.55	72	46	9
18 grms. dextrose injected.			

[1] "The influence of mechanical factors on lymph-formation." This *Journal*, XVI. 255.

[2] That is supposing that no sugar escaped from the circulation. Since this condition is not fulfilled I purposely inject a slight excess of sugar (18 instead of 14 grams).

Time	Fem. art.	Portal vein	Inf. cava
12.15	70 mm. Hg.	120 mm. $MgSO_4$	18 mm. $MgSO_4$
12.20	90	108	17
12.30	98	97	14
12.45	98	82	22

We see that by this means we can almost entirely obviate the rise of capillary pressure produced by the injection of sugar.

We may compare with this the effect of a similar injection on the lymph-flow.

Dog, $10\frac{1}{2}$ kilos.
Lymph in 10 minutes.

4·6—3·2* || 1·5 || †3·5—7·2—6·8.

* Bled to 350 c.c.

† 25 grms. dextrose in 25 c.c. water injected.

Under these circumstances the lymph-flow is hardly increased at all, although the solution of sugar in contact with the endothelial cells is even more concentrated than in the first experiment, in which no previous bleeding had taken place. The only factor which is wanting in this second experiment is the rise of capillary pressure, and one must therefore conclude that this rise of capillary pressure is an essential condition for the increase in the lymph-flow to take place.

I would therefore explain the action of the second class of lymphagogues as follows. On their injection into the blood, the osmotic pressure of the circulating fluid is largely increased. In consequence of this increase, water is attracted from lymph and tissues into the blood by a process of osmosis, until the osmotic pressure of the circulating fluid is restored to normal[1]. A condition of hydræmic plethora is thereby produced, attended with a rise of pressure in the capillaries generally, especially in those of the abdominal viscera. This rise of pressure will be proportional to the increase in the volume of the blood, and therefore to the osmotic pressures of the solutions injected. The rise of capillary pressure causes a great increase in the transudation of fluid from the capillaries and therefore in the lymph-flow from the thoracic duct. Heidenhain pointed out that the lymphagogue effect of these substances was proportional to their osmotic pressures, and therefore to the figure obtained by dividing their osmotic coefficient by their molecular weight. Since the hydræmic plethora produced by the injection must be proportional to this amount, it follows that the

[1] Cp. Hamburger. *Zeitschrift für Biologie*, p. 259, 1890.

intracapillary pressure will also be proportional to the same quantity, and we see that all the facts brought forward by Heidenhain can be explained on the filtration hypothesis. This dependence of lymph-production on intracapillary pressures will be evident on referring to Figs. 1 and 2, Plate 1, in which the results of the four experiments quoted are shown graphically.

Heidenhain pointed out that the action of these substances on the urine was proportional to their action on the production of lymph. This is true if a large number of experiments are made. In any individual experiment, however, as might be expected, the lymph-production varies inversely as the flow of urine. When the kidneys are acting well, very little increase in the lymph-flow may be produced, since the increased amount of fluid in the blood is so rapidly carried off by the kidneys that there is at no time any very largely increased rise of capillary pressure and therefore no great increase in the lymph-flow. The following experiment may serve as an illustration of this point.

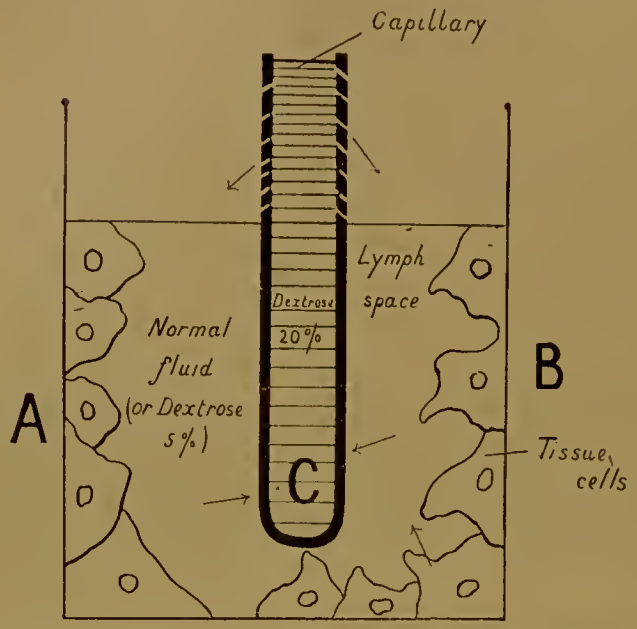
Dog, 8 kilos.
Lymph in 10 minutes.
1·5* || 3·5—7—5—3—2.

* Injected 20 grms. dextrose in 20 c.c. water. During the course of the experiment 300 c.c. urine were secreted.

There is one difficulty that might occur to readers of this article. Soon after the injection of the sugar there is a movement of water from the lymph-spaces into the blood to dilute the latter, at the same time that the capillary pressure and the transudation into the lymph-spaces are increased. There is no difficulty in reconciling this apparent contradiction, if we remember that the transference of the fluid in the two directions is due to two distinct physical processes. The transference of water from lymph-spaces and tissue-cells to the blood is due to a process of osmosis. The increased transudation from the blood into the lymph-spaces is occasioned by a process which at any rate is analogous to filtration. Perhaps a simple physical illustration will help to explain my meaning.

The vessel AB contains a 5 % solution of dextrose. Within this is a second vessel C, containing a 20 % solution of dextrose. The walls of the vessel C are composed of a semipermeable membrane (copper ferrocyanide for instance). Water will therefore pass from AB into C until the fluids in and outside the inner vessel have the same osmotic pressure. At the upper part of C however the wall is imperfect—it

contains pores, through which fluid will transude under a certain pressure. Thus water will pass from AB to C until the fluid in C



reaches a certain height and attains a certain pressure. From this point on there will be a movement of fluid in two directions—of water from AB to C by a process of osmosis and of the fluid in C (concentrated sugar solution) from C to AB by a process of filtration or transudation. This movement of fluid in the two directions will go on until the fluids in and outside C have the same composition. We might imagine that the endothelial cells themselves represented the semipermeable membrane, while the pores are represented by the spaces or clefts between the endothelial cells. Such a conception, however, must be merely a symbol of a possible explanation, since there are no facts either for or against it.

The First Class of Lymphagogues.

On injecting a decoction of cray-fish muscle or leeches into the blood, the lymph flowing from the thoracic duct is increased in amount and becomes much more concentrated than before. In both blood and lymph coagulability is lessened or abolished. The blood becomes more concentrated from a loss of plasma, while the plasma itself is less concentrated than before the injection. The blood-pressure, if the injection be carefully carried out, may be unaltered, although the heart as a rule beats rather more quickly than before. Heidenhain con-

cludes that these bodies exert a specific influence on the endothelial cells, causing them to secrete an increased amount of the lymph more concentrated than the blood-plasma. In investigating the action of these bodies, one is struck at the outset with the marked analogy that exists between the effects of their injection and the effects produced by a purely mechanical means, i.e. obstruction of the inferior vena cava above the diaphragm. In the latter, as in the former case, we have an increased production of concentrated lymph while the blood becomes more concentrated and the blood-plasma more watery. I have shown in the previous paper[1] that the whole increase in the lymph observed after obstruction of the inferior cava is derived from the liver, and that all the effects of this obstruction are explained by the fact that there is a greatly increased production of concentrated lymph in the liver. The question arises whether the same explanation may not hold good for the effects observed after the injection of cray-fish extract or peptone. To decide this question, I ligatured in a number of cases the portal lymphatics before the injection of the lymphagogues. The effect of this procedure on the results of the injection, although striking, is in most cases not so absolute as I had found it to be on the results of obstructing the vena cava. If the portal lymphatics be ligatured and the vena cava obstructed, the lymph remains practically unaltered in quantity and composition. In the following experiments, it will be seen that in some instances this was also the case; in others, however, there was a slight increase in the amount and also in the concentration of the lymph. One must remember, however, that the lymph from the interior of the liver has two ways open to it. Although the majority of the lymphatics leave the liver at the portal fissure, there are some which accompany branches of the hepatic vein and leave the liver with these veins. When the vena cava is obstructed just above the liver, it is probable that these latter lymphatics are also obstructed, so that ligature of the portal lymphatics absolutely shuts off the liver-lymph. When lymphagogues are injected into the circulation, after ligature of the portal lymphatics, the lymph can still pass along the hepatic vein lymphatics, and we shall get a certain amount of liver-lymph according to the degree in which these lymphatics are developed. I give therefore a number of protocols in order to show that ligature of the portal lymphatics has a considerable, and in some cases, an absolute effect on the results of the injection of lymphagogues.

[1] This *Journal*, xvi. 234.

I. Injection of decoction of mussels.

A. Portal lymphatics free.

(1)	Lymph in 10 mins.	3·6	3·6*	26	23	21	19·6	16	13 c.c.
	Total solids in lymph	4·93%		5·94%	5·89%				5·38%

B. Portal lymphatics ligatured.

(1)	Lymph in 10 mins.	2·8	3·2*	3	4	3·2 — 2·8 c.cm.
	Solids in lymph	3·53%		3·88%		3·73%

* A decoction of mussels injected into jugular vein.

II. Injection of peptone (·5 grams pro kilo.).

Portal lymphatics ligatured.

(1)	Lymph in 10 mins.	5*	3·2†	6·2	5·6	4·5	4	
	Solids in lymph	6·08%	5·28%		5·60%	5·62%		
(2)	Lymph in 10 mins.	2·4	2†	4	5·2	3·4	2·8	2·6
	Solids in lymph	6·1%		7·6%				
(3)	Lymph in 10 mins.	2·2	2	1·8†	3·6	3·6	2·6	2·2	1·8 c.c.
	Solids in lymph	4·65%			4·90%	5·24%			

* Portal lymphatics ligatured. † Peptone injected.

III. Injection of decoction of cray-fish muscles.

A. Portal lymphatics free.

(1)	Lymph in 10 mins.	2·5	2·4*	10	8	7·5	7 c.c.	
	Solids in lymph	5·3%		6·5%				
(2)	Lymph in 10 mins.	3·8	3·5*	17·4	12·4	10	9	10	6·2 c.c.
	Solids in lymph	5·37%		6·53%			6·21%		

B. Portal lymphatics tied.

(1)	Lymph in 10 mins.	1	1*	1	2·2	2·6	2·2	2 c.c.
	Solids in lymph	6·05%		5·81%		5·84%		
(2)	Lymph in 10 mins.	6·6	5*	7·6	16	8·2	7·8	7·8	7·2 c.c.
	Solids in lymph	4·79%		5·15%			4·80%		
(3)	Lymph in 10 mins.	2·7	2*	3	3·4	2·6	3	3·4	3·6	3·8 c.c.
	Solids in lymph	5·46%		5·88%					6·07%

* Decoction of cray-fish muscles injected.

In these protocols I would draw attention to the fact that, when the portal lymphatics are free, the greatest increase of lymph is obtained in the first ten minutes after injection. In those cases where an increased flow of lymph is observed even with ligatured portal lympha-

tics, the greatest increase is observed in the second or third period of ten minutes after the injection; suggesting that the lymph has had to make its way through unaccustomed and narrow paths before arriving at the thoracic duct.

I think a study of these experiments shows conclusively that the greater part, if not the whole, of the increased lymph-flow obtained after injection of lymphagogues of the first class is derived from the liver.

This fact in itself seems to explain many of the facts first observed by Heidenhain and interpreted by him in favour of the secretory hypothesis. The lymph is more concentrated because it is produced by the permeable capillaries of the liver, where, under all circumstances, the lymph is more concentrated than the ordinary mixed lymph flowing from the thoracic duct.

The blood becomes more concentrated because it loses a large amount of its plasma in the liver.

The blood-plasma becomes more watery because there is a loss of concentrated lymph in the liver, and a gain of less concentrated lymph in other parts of the body[1].

There is no need to assume, as Heidenhain does, that a fluid more concentrated than the blood-plasma has left the blood vessels; and therefore one of the chief arguments for the secretory hypothesis falls to the ground.

We have now to inquire why and how the injection of lymphagogues causes an increased formation of lymph in the liver. In all the cases of increased lymph-production that we have hitherto studied, the increase could be accounted for by an increased pressure within the capillaries of the organ affected. Is that the case here?

All the substances belonging to the first class of lymphagogues, if injected in sufficient quantities, cause a lowering of arterial pressure and affect the heart injuriously. This effect varies in the different members, being most pronounced in the case of peptone, and least in the case of cray-fish extract. Heidenhain mentions as a possibility that the weakening of the heart's action, after the injection of peptone, might act like an obstruction of the inferior vena cava above the diaphragm and cause congestion of the abdominal organs. He rejects this however as a cause of the increased lymph-flow, since the increased flow may be obtained without any fall of arterial pressure (by injecting the peptone very slowly into the aorta). But in any case a heart failure, caused by the injection of any of these bodies, could not cause

[1] Cp. this *Journal*, XVI. 255.

any large increase in the lymph-production. Bayliss and I have shown that complete stoppage of the heart causes very slight or no rise of pressure in the hepatic capillaries[1], unless there is at the same time a diminution of the capacity of the vascular system in consequence of a general vascular constriction. After the injection of peptone and other members of this group, the arterioles are relaxed and not constricted, so that all conditions are wanting for a rise of pressure to be caused by a failure of the heart.

I have made a large number of experiments with a view to determining the action of peptone, mussel extract, and cray-fish extract on the circulation. In these the blood-pressures were determined simultaneously in the femoral artery, portal vein, and vena cava (through iliac vein). The methods employed were the same as those used by Bayliss and myself in the paper I have just quoted[1].

In most cases the solution employed causes a temporary fall in the arterial pressure, which may last from 1 to 20 or even 40 minutes according to the nature of the body injected. With cray-fish or mussel extract even the temporary fall may be wanting. In all cases however the heart beats more frequently after than before the injection.

In all cases, whether the arterial pressure fall or not, there is a rise of pressure in the portal vein, a rise amounting to from 40 to 60 mm. $MgSO_4$ solution. This rise of pressure lasts a considerable time; the portal pressure then gradually returns to normal, and reaches this point from 20 minutes to 1 hour after the injection.

The pressure in the vena cava is practically unaffected. When there is a great fall of arterial pressure, there may be some rise in the vena cava pressure, but this rise never lasts more than a few minutes. In most cases the pressure in the vena cava is unaltered by the injection.

Some observations by my friend Mr W. M. Bayliss may be also mentioned as throwing light on changes in the circulation in the limbs produced by the injection of these bodies. In his experiments the volume of the hind limbs was measured plethysmographically at the same time that the blood-pressure was recorded by a mercurial manometer connected with the carotid artery. On injection of mussel extract there was a fall of arterial pressure accompanied by an *expansion* of the limbs. As the arterial pressure gradually recovered itself, the limbs expanded still further, showing that the recovery was not due to constriction of the limb vessels.

We may interpret these results as follows:

[1] "Observations on venous pressures." This *Journal*, XVI. 159.

When a moderate dose of mussel extract is injected into the jugular vein, the first effect is a general dilatation of the vessels in the body, which is especially marked in the splanchnic area. This in itself would tend to cause a fall of pressure, and in many cases we find that a fall does take place. In other cases however (and this is the rule with cray-fish extract) the heart beats faster and more powerfully, so that the dilatation of the vessels is compensated for and the arterial pressure remains normal, while the portal pressure is raised.

If a larger dose of the poison be injected, the heart muscle is also affected, and we get a lasting fall of arterial pressure, with a very weak heart-beat.

Are these changes in the vascular system sufficient to account for the increased production of lymph in the liver? I think we must answer this question in the negative, for the following reasons.

1. The increased lymph-flow after the injection of mussel extract lasts from 40 min. to 2 hrs. The rise of portal pressure caused by the injection of this substance is generally over in 20 to 40 min., and in no case have I observed a rise of portal pressure lasting more than one hour after the injection[1].

2. After the injection of these lymphagogues, the dilatation of the splanchnic vessels must occasion a certain rise of pressure in the capillaries of the intestines, and to a less degree, in the hepatic capillaries. I have shown above that the greater part of the lymph produced after the injection of lymphagogues is derived from the liver. Now under no circumstances, after the injection of lymphagogues, can the capillary pressure approach the amounts observed after obstruction of the inferior vena cava, and yet one may obtain as large a lymph-flow on injection of lymphagogues as on obstruction of this vessel.

Taking these two facts into consideration, we must conclude that the increased lymph-flow observed after injection of lymphagogues of the first class cannot be accounted for by increased capillary pressure. It is

[1] I have tried in vain to imitate this rise of portal pressure by division of both splanchnic nerves. I am inclined by these experiments and by the results, described later on, of long-continued obstruction of the aorta, to ascribe the rise of portal pressure observed after the injection of these lymphagogues, not to the splanchnic dilatation, but to an increased resistance in the capillaries of the liver, similar to that which occasions stasis in inflammation of other parts of the body. The capillaries might be said to become more 'sticky' in consequence of the injection. I would not however lay too much stress on this explanation of the rise of portal pressure, since I do not see my way at present to testing it experimentally.

open to us to conclude that these bodies act in Heidenhain's sense on the endothelial cells of the hepatic capillaries, exciting them to an active secretion of lymph. I have however shown that the other facts brought forward by this author in favour of the secretory nature of the process of lymph-production may be otherwise interpreted. After the injection of these lymphagogues, we have the same kind of lymph produced in the liver as is produced under all other circumstances. It would be simpler to explain the action of these bodies if we assume that they increase the permeability of the capillaries, so that a pressure, which is very little above the normal capillary pressure, is able to cause a greatly increased transudation of fluid. And it is only natural that these bodies, which act as poisons on the muscles of the heart and blood vessels and which, according to Löwit[1], Wright and others, cause a rapid disintegration of white blood-corpuscles, should also have a deleterious action on the endothelial cells of the hepatic capillaries. Heidenhain would regard the increased lymph-flow, after the injection of these lymphagogues, as a *physiological* reaction of the endothelial cells to a stimulus. According to my explanation, the increased flow would be a *pathological* phenomenon, dependent on injury to the capillary-wall. The effect of this increased permeability is moreover probably enhanced by the increased intracapillary pressure caused by the splanchnic dilatation.

There is one other argument in favour of the secretory hypothesis which we must now examine. Obstruction of the blood-supply to the kidneys for a few minutes stops the secretion of urine for a considerable time, in consequence of the injury to the secretory epithelium produced by the temporary anæmia. Obstruction of the thoracic aorta for 70 minutes or 2 hours causes a subsequent injection of any member of the first class of lymphagogues to be without effect on the lymph-flow from the thoracic duct. Heidenhain ascribes this negative result of the injection to injury of the endothelium caused by the long-continued anæmia, and concludes therefrom that lymph is a secretion.

On repeating these experiments, the first thing that strikes one is the difficulty of drawing any conclusions from them as to the nature of lymph-formation. In many cases the dog is in such a bad condition on releasing the obstruction at the end of the 2 hours, that one could not expect to obtain any definite results. If, however, large dogs be used and be kept warm during the obstruction, the arterial pressure

[1] *Studien zur Phys. und Path. des Blutes und der Lymphe.* This *leucolysis* is however rendered very dubitable by Sherrington's observations (*Proc. Roy. Soc.*, Vol. 55, p. 161).

may return to a fair height on releasing the obstruction. In these dogs, injection of cray-fish extract or peptone has no effect on the lymph-flow and, as a rule, very slight or no effect on the blood-pressure. Before drawing any conclusions however from these experiments, it is necessary to see what are the effects produced by the long-continued obstruction itself.

The following experiment will serve to illustrate the effect of this interference on the lymph-flow.

Time	Lymph in 10 mins.	Lymph	
11.0—11.10	3·6 c.cm.	3·6 c.cm.	Aorta blocked at 11.25[1].
11.25—1.25	1·6 „	17 „	Aorta released at 1.25.
1.25—35	6 „	6 „	(bloody)
35—45	9 „	9 „	„
45—55	9·2 „	9·2 „	„

We thus see that the lymph-flow falls during the obstruction, and when the obstruction is relieved, rises to considerably above its original amount, although the arterial pressure is much lower than at the beginning of the experiment.

Much more striking are the effects of the obstruction on the abdominal circulation. I give here a protocol of an experiment in which the pressures were registered simultaneously in the femoral artery, portal vein and inferior vena cava.

Dog, 15½ kilos. Consecutive readings at one minute intervals.

Time	Fem. art.	Portal vein	Vena cava
	96	100	30
	96	100	30
12.0 midday	*12	51	36
	8	48	36
	8	51	44
	8	54	44
	8	54	44
1.0 p.m.	9	52	42
2.0 p.m.	9	49	30
	†75	180	26
	74	260	36

* Aorta obstructed. † Obstruction relieved.

[1] Here, as in all other cases, the aortic obturator was introduced through the right carotid artery.

Time	Fem. art.	Portal vein	Vena cava
2.0 p.m.	67	230	34
	63	200	32
	60	180	32
	60	176	32 etc.
2.7 p.m.	54	130	32
2.30 p.m.	60	88	32
	*—	—	— (no reading)
	34	176	228
	32	186	234
	30	182	228
	30	180	216
	28	170	204

* Inferior vena cava obstructed above diaphragm.

It will be seen that, on releasing the aorta, while the arterial pressure returns to somewhat over half its original height, there is an enormous rise of pressure in the portal vein—a rise comparable with that obtained in other experiments after obstruction of the inferior vena cava above the diaphragm, and exceeding that produced by a subsequent obstruction of the vena cava. Of course the long-continued anæmia causes a paralysis of the splanchnic vessels and consequent vascular dilatation, but no amount of splanchnic dilatation will account for the rise of pressure observed here in the portal vein. That the rise is not due to backward pressure from the heart is shown by the absence of rise in the vena cava. There must in fact be considerable obstruction in front of the portal vein, that is to say, to the flow of blood through the liver. We can hardly imagine that the effect of the anæmia on the branches of the portal vein in the liver would differ from its effect on the intestinal vessels, and so cannot ascribe this rise of portal pressure to constriction of these branches. The resistance must therefore be in the capillaries; the hepatic capillaries are so altered that the resistance in them is very largely increased. By application of suitable means, we can alter the capillaries in any part of the body, so that stasis is produced in them, and I consider therefore that the long obstruction of the aorta has injured the capillaries of the liver, in exactly the same way as the application of croton oil will injure the capillaries of a frog's web.

In the experiment just quoted, the pressure in the portal vein, after rising to 260 mm., gradually fell to 88 mm. This fall might be due to a

giving way of resistance in the liver, or to a diminution of the amount of blood flowing into the portal vein. It is probably due to both factors. The presence of the second factor is, I think, rendered probable by the behaviour of the blood-pressures on subsequent obstruction of the inferior vena cava. In a normal animal, on obstruction of the inferior cava above the diaphragm, the pressure in the portal vein rises to a maximum within 10 secs. after the obstruction is complete. If however the aorta has been previously obstructed for two hours, the pressure rises much more gradually, attaining its maximum at the end of a minute or two, as in the experiment quoted, or, as in another experiment, not reaching its maximum until 4 min. after the obstruction. This diminution of the flow into the portal vein must be due to an increased resistance in the capillaries between arteries and portal vein, and here the injured condition of these vessels is extremely evident. On opening the abdomen of these dogs at the end of the experiment, the intestines appear distended, although the animal has received no solid food for the last 24 hours. On cutting them open, they are seen to be filled with a yellow pasty mass, while the mucous membrane is in an extreme condition of inflammatory congestion and in many places quite black. Often the pasty contents are mixed with effused blood. On examining the contents under the microscope, they are seen to consist entirely of desquamated epithelial cells. We have here, in fact, an exquisite example of Cohnheim's experiment on the production of inflammation by anæmia.

It is evident now why injection of these lymphagogues after obstruction of the aorta has no effect. I have shown above that their action may be ascribed to an injury of the vascular endothelium. After long-continued obstruction of the aorta, this endothelium is damaged to a much greater extent than could be effected by any injection of these lymphagogues and, just as we cannot kill a dead dog, so, by the injection of these lymphagogues, we cannot alter the permeability of the damaged endothelium.

As might be expected, since the abdominal vessels are already completely paralysed by the long-continued anæmia, the injection of these lymphagogues can cause no further alteration in the blood-pressure, either in the arteries or in the portal vein. If the injection be excessive, there is a gradual fall of pressures in consequence of heart-failure.

If by any means we raise the pressure in the abdominal capillaries, such as by obstruction of the portal vein or inferior cava, or by injections

of solutions of sugar, we can still produce a corresponding rise in the transudation of lymph and in the lymph-flow from the thoracic duct. Since, however, the blood-flow from the liver is not so great as under normal circumstances, we cannot, by obstruction of the inferior vena cava, produce so large an increase in the lymph-flow as we usually get in consequence of this procedure.

Thus a renewed investigation of the facts discovered by Heidenhain has shown that they are not irreconcilable with the filtration hypothesis. One fact remains to be mentioned; viz. that, after the injection of sugar, etc. into the blood, the percentage amount of these bodies in the lymph from the thoracic duct rises higher than that in the blood-plasma. The question of the chemical composition and osmotic pressure of the lymph under various conditions I hope to consider in a future paper. I would here merely point out that we do not know how far the composition of the lymph from the thoracic duct represents that of the lymph as it is turned out from the vessels into the tissue-spaces. Its composition *must* in fact be determined to a certain extent by the tissue-cells, and we cannot at once with certainty deduce a secretory activity of the endothelial cells from differences in the composition of thoracic duct lymph and blood-plasma.

I have devoted so much attention to showing that the secretory hypothesis of lymph-formation is unnecessary, that I think I ought to emphasise the fact that my experiments are merely a continuation and not a refutation of those of Heidenhain. Not a single experimental result in his paper[1] but I have been able to confirm. Indeed to Professor Heidenhain's work and teaching I am indebted for all the results that I have succeeded in obtaining.

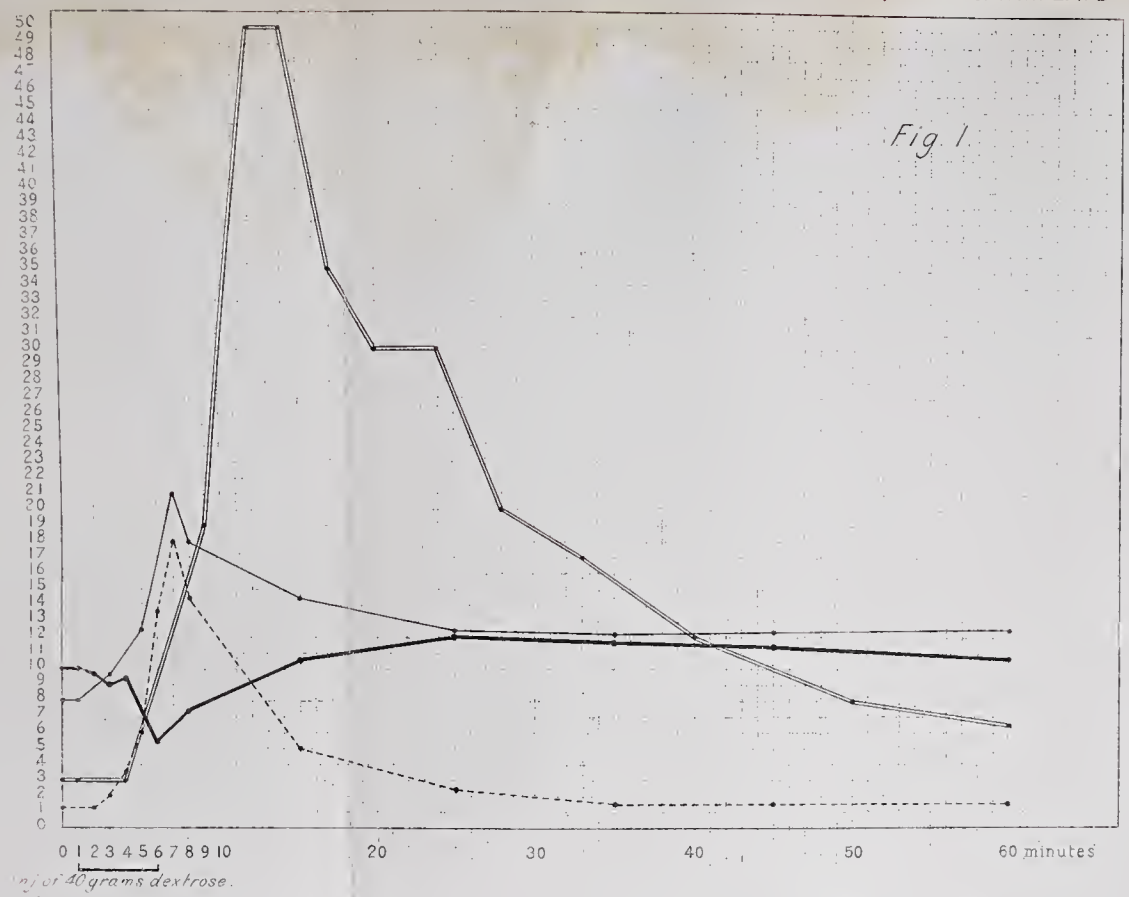
Conclusions.

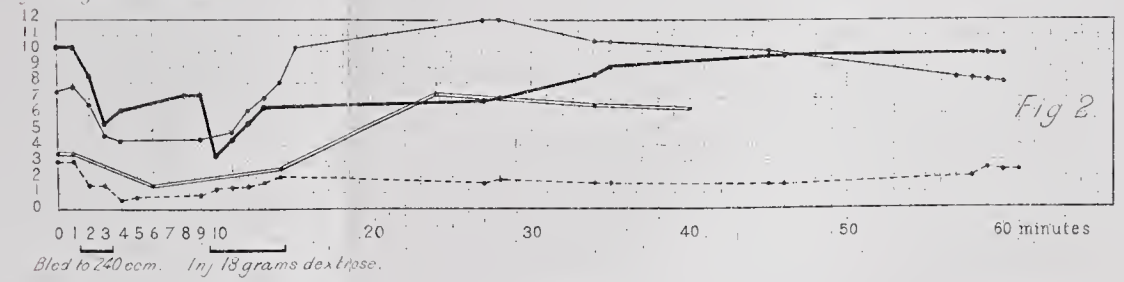
(1) Lymph-formation is a function of two factors, viz.—
Permeability of the vessel-wall and
Intracapillary blood-pressure.

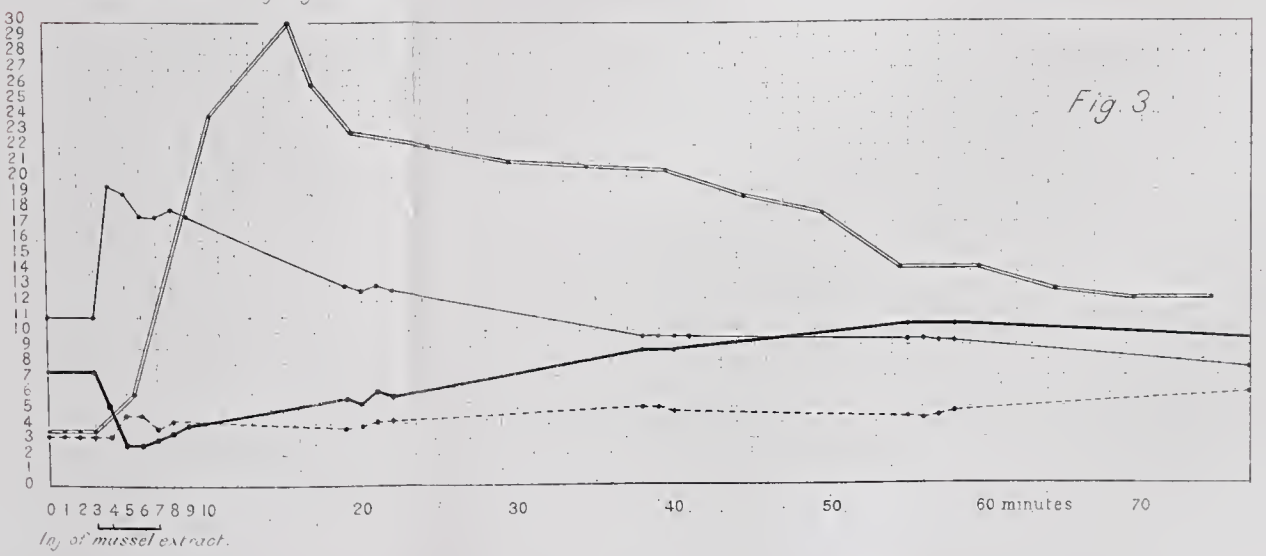
(2) Members of the second class of lymphagogues (sugar etc.), on injection into the blood, attract water from the tissues, and cause a condition of hydræmic plethora with increased capillary pressures.

The increased lymph-flow from the thoracic duct is due to the increased pressure in the abdominal capillaries.

[1] *Pflüger's Archiv*, xlix. 209.







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(3) Members of the first class of lymphagogues affect injuriously:

First, the endothelial cells of the capillaries, especially in the liver, increasing their permeability.

Secondly, the muscular walls of the blood vessels, especially in the splanchnic area, producing vascular dilatation.

Thirdly, the heart muscle.

The increased flow of lymph is due to the increased permeability of the hepatic capillaries, nearly the whole of the increased lymph-flow being derived from the liver.

PLATE I.

In all three curves the divisions of the abscissa indicate minutes.

Each division of the ordinates expresses:

(*a*) Rate of flow of lymph (in c.cm. in 10 minutes).

(*b*) Height of pressure in femoral artery (in cm. Hg).

(*c*) Height of pressure in portal vein and vena cava (in centimetres $MgSO_4$ solution).

Each curve represents two experiments, one in which the three pressures were recorded, and a similar one in which the lymph-flow and the arterial pressure were recorded. In each case experiments were chosen in which the arterial pressures underwent corresponding changes.

The double line = rate of lymph-flow.

The thick line = pressure in femoral artery.

The thin line = pressure in portal vein.

The dotted line = pressure in inferior vena cava.

Fig. 1. Rate of lymph-flow and pressures after injection of sugar (renal vessels ligatured).

Fig. 2. Rate of lymph-flow and pressures after bleeding to 240 c.cm. and injection of 18 grams dextrose.

Fig. 3. Rate of lymph-flow and pressures after injection of decoction of dried mussels.

June 4, 1894.